

Fourier transform molecular rotational resonance spectroscopy for reprogrammable chemical sensing

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ABSTRACT

Molecular rotational resonance (MRR) spectroscopy gives spectral signatures with high chemical selectivity. At room-temperature, the peak intensity of the MRR spectrum occurs in the 100 GHz – 1 THz frequency range for volatile species with mass \leq 100 amu. Advances in high-power sub-mm-wave light sources has made it possible to implement time-domain Fourier transform (FT) spectroscopy techniques that are similar to FT nuclear magnetic resonance (FT-NMR) measurements. In these measurements, the gas sample is excited by a short (200 ns) excitation pulse that creates a macroscopic sample polarization. The electric field of the subsequent transient molecular emission is detected using a heterodyne receiver and a high-speed digitizer. FT-MRR spectroscopy offers speed and sensitivity improvements over absorption spectroscopy. For chemical analysis, FT-MRR spectrometers combine the benefits of broad chemical coverage typical of gas chromatography – mass spectrometry (GC-MS) instruments and the direct measurement capabilities of infrared gas sensors all in a reprogrammable platform. Pulse sequence measurements can be implemented for advanced spectroscopic analysis. Trace level quantitation of volatile species at ppbv concentration can be performed on the time scale of a minute. In cases where the sample is a complex mixture, a double-resonance pulse sequence can be used to achieve chemical selectivity even in cases where spectral overlap occurs. These measurement capabilities are illustrated using the application of FT-MRR spectroscopy to residual solvent analysis of pharmaceutical products.

Keywords: spectroscopy, rotational spectroscopy, volatile organic compounds, residual solvent analysis, process analytical technology, headspace analysis, millimeter wave, terahertz

1. INTRODUCTION

1.1 The development of broadband FT-MRR

The recent development of Fourier transform (FT) techniques for millimeter wave spectroscopy has provided performance advances for molecular rotational resonance (MRR) spectroscopy that make it applicable to a wide range of analytical chemistry applications.¹⁻⁷ The strengths of MRR among molecular spectroscopy techniques are its high spectral resolution and structure specific fingerprint, which enable chemically selective, direct mixture analysis. Although decades of scientific literature have brought attention to the capabilities of MRR for chemical analysis, conventional techniques (based on absorption) have been limited in terms of measurement speed and sensitivity.⁸⁻¹³ The only previous MRR product line was a microwave spectrometer (8 – 40 GHz) offered from Hewlett Packard in the 1960s.¹⁴⁻¹⁶ With the introduction of broadband millimeter/submillimeter active multiplier chains (AMCs) that use cascaded Schottky diode multipliers, the room temperature MRR spectrum can be measured in its most favorable frequency region (100-1000 GHz) using stable low frequency microwave synthesizers as the input light source.¹⁷ FT-MRR instruments best utilize the high power sources (>25 mW) to perform sensitive spectroscopy on room-temperature gases, reaching the same sensitivity level 10,000 times faster than the fastest absorption-based AMC driven spectrometers described in the literature.^{1,18-21} The advantages of FT-based millimeter wave techniques are similar to those of Fourier transform nuclear magnetic resonance (FT-NMR) over absorption methods. As in FT-NMR, a variety of pulse sequences can be applied to extract more information than the ordinary absorption spectrum can provide.²² These tools further enhance the analysis capabilities of FT-MRR.

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A molecule's rotational spectrum is one of the most chemically selective fingerprints; it is structure specific and highly resolved at low pressures (< 100 mTorr).^{8,23} Small changes in the mass distribution of a molecule affect the rotational inertia enough to give resolved rotational spectra. As a result, isomers, isotopologues, conformers, and vibrationally excited states contribute distinct FT-MRR spectra, which can lead to spectral confusion at dynamic range of ~1000:1 or greater, and weak emission can occupy every data channel across the band. Since analytical methods are predominantly concerned with impurity analysis, the ability to confidently detect weak components against the sample matrix is essential. Broadband FT-MRR spectroscopy (e.g. 30 GHz of bandwidth) makes use of the spectral redundancy of the repeating rotational pattern to perform a multi-point identification and quantification through library matching.^{1,3-5} With nearly 100,000 independent data channels, the chance of overlap for all of the strong features of a molecule's spectrum is extremely low. The broadband analysis is ideal for analyzing the composition of an unknown matrix, and its implementation for chemical analysis is described in a previous publication.³ For routine impurity analysis, on the other hand, it is often known what compounds are of importance. Therefore, it is more efficient to target specific spectral transitions and allocate the measurement time only for the analytes of interest. If the sample matrix is well known, frequencies that are free of spectral interference can be selected by consulting the spectral library.

The development of this targeted spectroscopy method has two major cost advantages in the hardware required. Broadband FT-MRR millimeter-wave instruments use high-speed arbitrary waveform generators (AWGs) to generate linear frequency sweeps (chirped pulses) for sample excitation in order to measure the full spectrum of the millimeter wave device (typically >30 GHz) in as fast as 2 μ s.⁵ When only single frequency excitation is required, the high-performance AWG can be replaced with tunable, integrated circuit (IC) microwave synthesizers, which have been shown to have sufficient phase stability and spectral purity for millimeter-wave spectroscopy.^{1,2,7} The second hardware advantage is the reduced requirement for digitizer sampling speed; since only a narrow frequency range is detected, the digitizer utilized for broadband spectroscopy (4 GS/s) can be replaced with a lower-digitization rate version (100 MS/s).

The tradeoff for targeted, single-line monitoring is the higher risk for false positive detection in the event of an unanticipated spectral overlap. In cases where many analytes are present across a large dynamic range, spectral interferences may be unavoidable. For most analytical sensors, all that can be reported is an upper limit to the concentration, since the detector response is a sum of all interfering analytes. However, FT-MRR can be used to selectively modulate a molecular carrier contribution in a region of spectral overlap at the frequency being monitored using double resonance excitation. In this paper, we apply a static headspace FT-MRR method for pharmaceutical residual solvent analysis to benchmark its performance for sensitivity, direct chemical selectivity, and selective double resonance excitation. We find that the selective modulation capability allows for the chemical selectivity and quantitative accuracy of broadband FT-MRR spectroscopy to be maintained in a complex sample matrix where spectral overlap occurs.

1.2 The analytical challenge for residual solvent analysis

United States Pharmacopeia (USP) general chapter 467 defines GC-FID/MS headspace analysis as the standard method against which new methods for residual solvent analysis must be verified.²⁴ Generally, high throughput industrial process analyses are incompatible with the measurement characteristics of chromatographic techniques. Fast, simple spectroscopic solutions are desired. Since 2004, the pharmaceutical manufacturing industry has adopted the process analytical technology (PAT) initiative to incorporate quality by design manufacturing.^{25,26} Analytical methods are designed along side drug scale up to monitor critical quality attributes during the manufacturing process. Residual solvent content has become a critical quality attribute that generates a need for high throughput impurity analysis.²⁷ The ICH guidelines for residual solvent analysis classify 59 commonly used solvents in pharmaceutical manufacturing into three groups: Class I, highly toxic solvents which should be avoided; Class II, moderately toxic solvents which should be limited in use; and Class III, low toxicity solvents.²⁷ Depending on toxicity, the allowable limit can range from 0.5% to 0.005% by mass assuming a daily dosage of 10 g, and the total solvent content must be no more than 0.5%. Only the solvents known to be used (or produced) during synthesis need to be quantified. However, there are usually several solvents present. When factoring in calibration runs, blank runs, and analysis, a residual solvent analysis by gas chromatography can take several hours. The typical sample preparation procedure involves dissolving a small amount of active pharmaceutical ingredient (API) or intermediate into a low vapor pressure solvent (e.g. DMAC - N,N Dimethylacetamide) at 10-50 mg/mL and sampling the headspace after equilibration. When two solvents happen to co-elute, further method development is necessary in order to resolve them. This can be the case for very low vapor pressure solvents which interfere with the diluent elution, and for very high vapor pressure solvents which elute together. The full panel of solvents may require the development of several different chromatographic methods. Because most of

the 59 regulated solvents fit into the FT-MRR niche of small, polar, volatile molecules, residual solvent analysis is an ideal match to the strengths of targeted FT-MRR spectroscopy which can produce high dynamic range spectra in seconds.

2. EXPERIMENTAL

2.1 FT-MRR sampling methodology

A major distinction for the FT-MRR sampling path is that it relies on the vacuum of the sample cell to pull in an aliquot of the higher pressure headspace. No carrier gas is required. The sample is introduced to the system by injecting 0.5 mL of the dissolved API solution into an evacuated standard headspace vial (in the measurements presented here, 27 mL volume). After allowing the headspace to equilibrate (for 2 minutes), an aliquot of the headspace above the solution is transferred into the spectrometer's sample chamber via a valve/loop mechanism shown in Figure 1. To minimize chemical carryover, Dursan® coating in combination with elevated temperature is used in the sample cell (40 °C) and sample transfer lines (60 °C). In addition, moderate heating of the vial (to 50 °C) significantly enhances the headspace vapor concentrations for most of the residual solvents tested.

The volume of the sample loop is chosen such that the total pressure in the sample cell is maintained below 100 mTorr (above which pressure broadening sacrifices the resolution and sensitivity of the technique). At these low pressures, the mixture behaves as an ideal gas where the spectrum of the analyte and its partial pressure is independent of the matrix. The most common diluents used for GC headspace analysis are dimethylformamide (DMF), N,N-dimethylacetamide (DMAC), 1,3-dimethyl-2-imidazolidinone (DMI) and dimethyl sulfoxide (DMSO), chosen for their dissolving strength and their low vapor pressure. Low volatility diluents are used so that they elute very late off of the column, minimizing interference with analytes. Static headspace FT-MRR analysis also benefits from low vapor pressure diluents because they enhance the analyte concentration in the headspace.

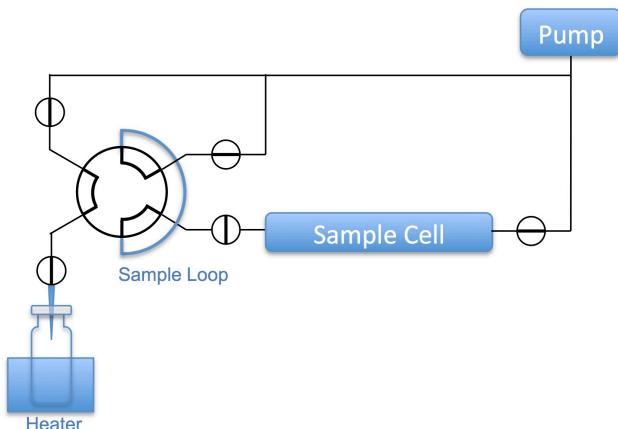


Figure 1. The static headspace FT-MRR sampling module equipped with a valve/loop loading mechanism. Mixtures equilibrate into the vacuum of the headspace vial. Then, a fixed volume of headspace fills a sample loop for transfer to the sample cell via 6-way valve. The sample loop volume ensures a total pressure in the sample cell of less than 100 mTorr.

Table 1: Static Headspace FT-MRR Measurement cycle time

Procedural Step	Time
Evacuate vial	2 minutes
Inject and equilibrate	2 minutes
Transfer headspace sample	5 seconds
Measure FT-MRR spectrum	10 - 60 sec/analyte
Total	~ 5 minutes

The broadband FT-MRR spectrumThe AWG driven broadband FT-MRR spectrometer, which is described in more detail elsewhere,³ was used to analyze the headspace of a solvent mixture composed of ten solvents dissolved in DMAC at

approximately 0.1 mg/mL each (prepared by ChemService, Inc. with a GC verified composition at 1 mg/mL, and further diluted by a factor of 10). The results are presented in Figure 2. This measurement set the expectations for sensitivity and signal overlap (see Figure 2). The set of analytes were chosen for their common use as solvents in pharmaceutical manufacturing and the fact that they have a non-zero dipole moment – a requirement for rotational spectroscopy. USP 467 calls for the preparation of solutions with 10 mg of API per 1 mL of diluent, so the mixture analyzed in Figure 2 would correspond to solvent impurities at 1% w/w in a solid. The broadband spectrum in Figure 2 was acquired in 10 minutes, and the noise level in this spectrum is 0.6 μ V.

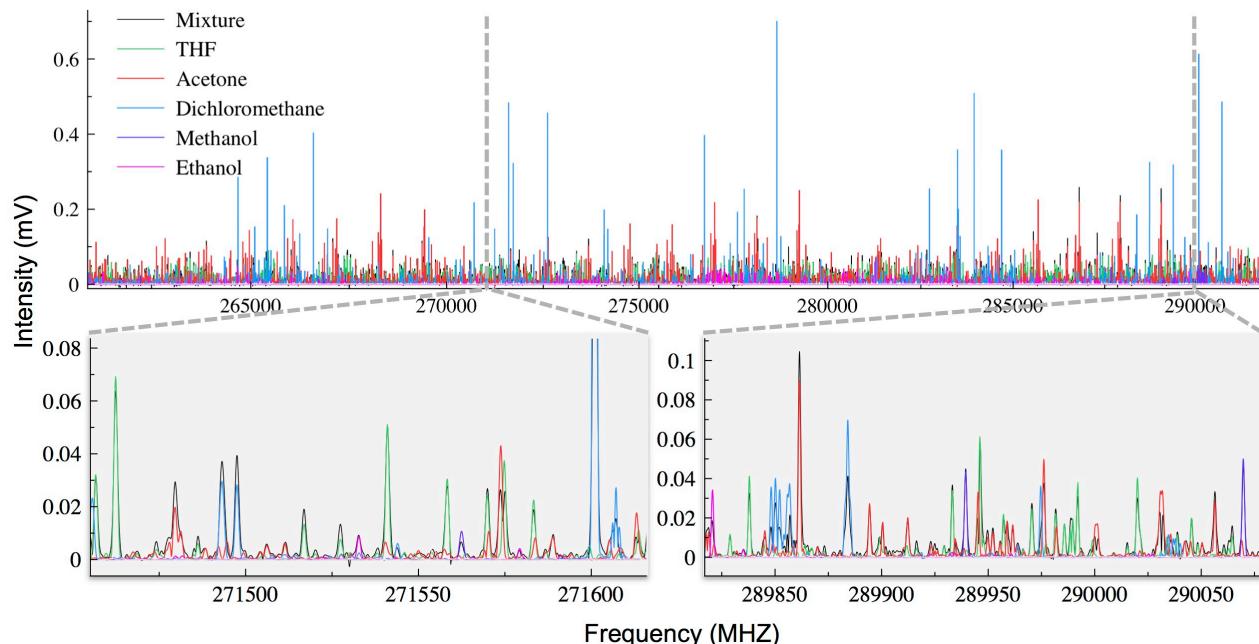


Figure 2. A broadband library matching analysis (colors) of the headspace mixture (black) of several solvents dissolved in N,N dimethylacetamide at approximately 0.1 mg/mL. The full spectrum (top), acquired in ten minutes, illustrates the repeating spectral patterns of components in the mixture. Although DMAC is a major component of the vapor, its weak MRR spectrum does not hurt the dynamic range of the analysis. The expanded view of the data set (bottom) illustrates the spectral isolation despite the complexity of the mixture.

2.2 Targeted, double resonance modulation using low cost microwave synthesizers

The instrument schematic for microwave generation, upconversion, multiplication to millimeter wave frequencies, and heterodyne detection is essentially the same for the targeted FT-MRR spectrometer and the AWG driven spectrometer (shown in Figure 3). In place of the AWG, we use a pulse modulated microwave light source design similar to one developed at the University of Virginia for millimeter wave double resonance excitation (see Figure 4).^{2,7} Since these are free-running synthesizers, consideration must be given to the frequency tuning. FT-MRR is a time-resolved technique where high sensitivity is achieved by co-adding consecutive free induction decays (FIDs) of molecular emission. This requires phase reproducibility with each excitation pulse, since the phase of the molecular FID is related to that of the excitation. For free-running synthesizers the allowable frequency resolution is limited by the smallest frequency step of the synthesizer and the requirement that it be phase commensurate (after multiplication) with the time interval for excitation. The Valon Technologies 5007 dual channel synthesizers integrated in our design have a minimum frequency step of 2.5 kHz, setting the first constraint after x24 frequency multiplication in the AMCs to 60 kHz integer multiples. We also choose an excitation time interval of 10 μ s where integer multiples of 100 kHz are phase commensurate. The result is 300 kHz resolution, meaning excitation is achieved at most 150 kHz off resonance (less than 6% the typical full width half max of a FT-MRR spectral line at 275 GHz).

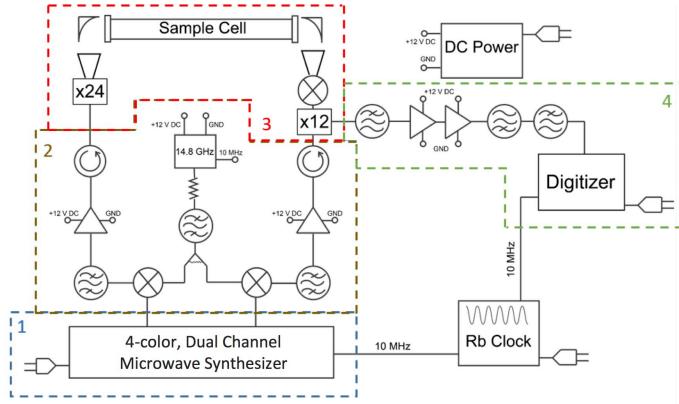


Figure 3. A block schematic of the FT-MRR spectrometer for targeted spectroscopy. The AWG is replaced with a 4-color, dual output microwave synthesizer source (1) that produces a pulse modulated, 2-color excitation waveform and local oscillator sinusoid between 2.5 – 4 GHz (illustrated in Figure 4). The output is upconverted (2), multiplied to millimeter wave frequencies (3) and then down converted in the heterodyne receiver for IF detection from 720 – 1440 MHz (4).

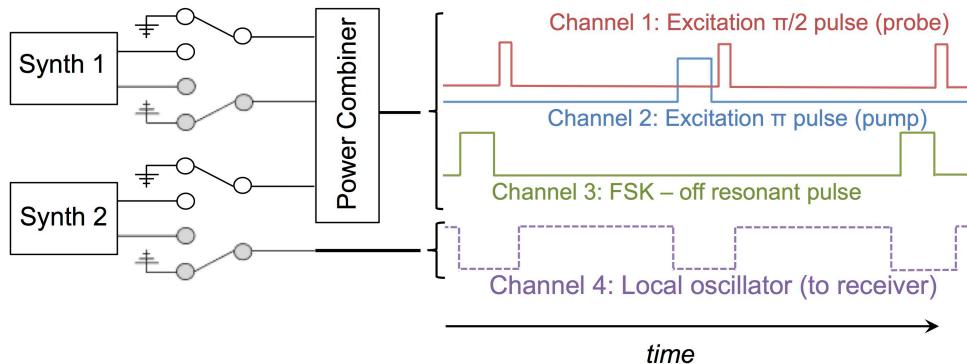


Figure 4. A schematic of the microwave light source in Figure 3 that generates 2.5 - 4 GHz for subsequent upconversion and input to the AMCs. Channels 1-3 generate the excitation waveform output - a probe excitation pulse preceded by a pump pulse that alternates off resonance to on resonance. The local oscillator from channel 4 drives the heterodyne receiver, but is modulated off during the high power excitation pulses so they do not saturate the IF amplifier.

The chemical selectivity of a targeted analysis can be enhanced with selective double resonance excitation and still retain the hardware advantages of targeted spectroscopy. In order to induce the double resonance effect, two connected spectral transitions within the band of the spectrometer are identified either by experiment or published line lists that include assignments of the rotational energy manifold.^{28,29} Then, the closest 300 kHz frequency integer multiple is chosen for resonant excitation of each transition. Four independently tunable microwave sources are required and each is modulated on/off by a fast single-pole, double-throw (SPDT) switch. The excitation scheme for double resonance is illustrated in Figure 4.

The principles of FT-MRR double resonance have been described elsewhere.³ The technique uses concepts from NMR spectroscopy, such as the $\pi/2$ and π pulse excitation conditions. However, in rotation spectroscopy the energy levels have a degeneracy arising from the spatial orientation (labeled by the M_J angular momentum quantum number). The Rabi frequency is M_J dependent, so the use of NMR terminology is an approximation. To summarize, in time domain Fourier transform spectroscopy, a resonant excitation pulse induces a macroscopic polarization that is a function of time and proportional to the population difference under thermal equilibrium (Δ) between the upper state and lower state of the transition. A pump pulse (generated by Channel 2 in Figure 4) applies resonant excitation to one of the transitions long enough to create a population inversion (π pulse), doubling the population difference in a connected transition to $\sim 2\Delta$.

Then, the probe pulse (Channel 1) excites the connected transition that is being monitored with the optimal $\pi/2$ duration. The FID emission from the probe transition is then detected and Fourier transformed with the ideal result of a 100% increase in signal intensity. Frequency shift keying (FSK) is used to account for variable power loads on the receiver between the probe and pump-probe acquisition. Channel 3 is used to generate an off resonance “pump” pulse shifted by 10 MHz. Any change in receiver response at the probe frequency due to load-bearing will interfere with the detection of true double resonance modulation. It is also beneficial to lengthen the time interval between the double resonance excitation sequences. This is accomplished by inserting two off resonant pumping sequences for every resonant pump. Without FSK (Channel 3 remains off), the response of the detector varies by 5 – 10% - a significant sacrifice in performance compared to the < 1% variation with FSK.

3. RESULTS AND DISCUSSION

3.1 Targeted single line monitoring

Table 2. FT-MRR sensitivity for solvents dissolved in DMAC.

Analyte	Frequency (MHz)	USP 467 limit ^a	FT-MRR MDL ^b (w/w) 50 °C
Ethanol	281279.84	5000 ppm	75 ppm
Acetone	279243.51	5000 ppm	25 ppm
2-Butanone	264591.51	5000 ppm	365 ppm
Methanol	278304.53	3000 ppm	55 ppm
Tetrahydrofuran	275459.54	720 ppm	50 ppm
Dichloromethane	278644.96	600 ppm	8 ppm
1-Propanol	270634.62	5000 ppm	940 ppm
2-Propanol	267669.01	5000 ppm	1230 ppm
Toluene	<i>not detected</i>		
Acetic acid	<i>not detected</i>		

a) For a 10 g daily dosage.

b) Method detection limit, with 5 seconds of signal averaging in targeted mode. Assumes a sample preparation with 10 mg of API dissolved per mL of diluent.

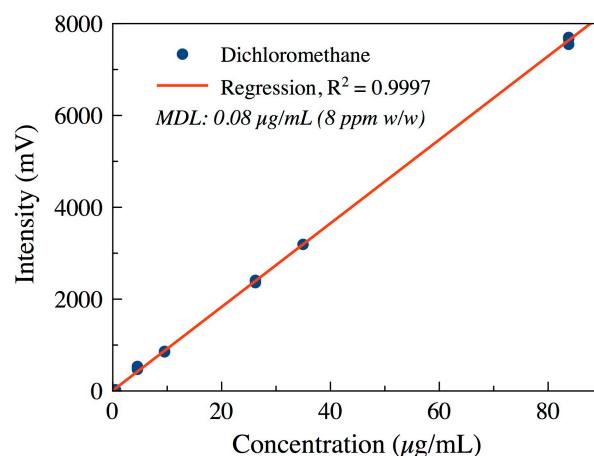


Figure 5. A plot of dichloromethane signal strength as a function of concentration in DMAC across 0.48 – 83 $\mu\text{g/mL}$ (0.0048 % – 0.830 % w/w by USP 467). The result shows excellent linearity and a five second detection limit of 8 ppm, well below that required for residual solvent analysis (600 ppm regulated upper limit by USP 467).

Sensitivities for solvents in the ten component mixture were determined using the AWG driven spectrometer for targeted spectroscopy (see Table 2). Dichloromethane, having the strongest signals in the mixture, was used to test the linearity of the instrument response. Analysis across a range of concentrations from 0.48 – 83 $\mu\text{g/mL}$ or 0.0048 % – 0.830 % w/w by USP 467 exhibits a linear correlation coefficient of 0.9997 (see Figure 5). Acetic acid and toluene are not detected at 83 $\mu\text{g/mL}$ concentrations. Although acetic acid is a favorable detection target for FT-MRR, it partitions poorly out of the solution phase, and is better detected by direct headspace analysis of the solid. The spectrometer is also sensitive enough to measure toluene at 83 $\mu\text{g/mL}$. Dilute solutions of toluene in DMAC have been used to show a detection limit of <0.1% w/w with one minute of signal averaging at 277978.9 MHz. However, the ten-component mixture used here provides a sufficiently dense background to interfere with toluene emission.

3.2 Double resonance modulation

The targeted frequencies in Table 2 were chosen in order to ensure there were no strong overlapping signals from other species in the matrix. This generally allows an interference free analysis, but without full knowledge of the matrix, a wide dynamic range cannot be guaranteed. Although each species in the ten component solvent mixture can be targeted in a region free of spectral overlap (as in Table 2), double resonance modulation was performed on a region that did have interfering emission to demonstrate the ability to FT-MRR to resolve overlapping features. The spectral region at 266838 MHz was chosen to demonstrate the detection of methanol by double resonance modulation in the presence of tetrahydrofuran (THF) interference. Methanol line centers and their associated rotational levels are known in the spectroscopy literature across a large range of frequencies.²⁸ We selected a pump pulse transition at 265289.68 MHz (transition quantum numbers $J_K = 6_1 - 5_2$ of the E symmetry species) and a probe pulse transition at 266838.00 MHz ($5_2 - 4_1 (E)$). Once the connected transitions were identified, the optimal excitation pulse durations are determined by monitoring each signal as a function of the pulse duration – the nutation curve. For maximum sensitivity of the probe signal, it is necessary to apply a $\pi/2$ excitation pulse for the probe transition – where the nutation curve is at its peak value. The oscillation back to a minimum in the nutation curve represents the π pulse duration where the maximum population inversion is achieved. The nutation results are displayed in Figure 6.

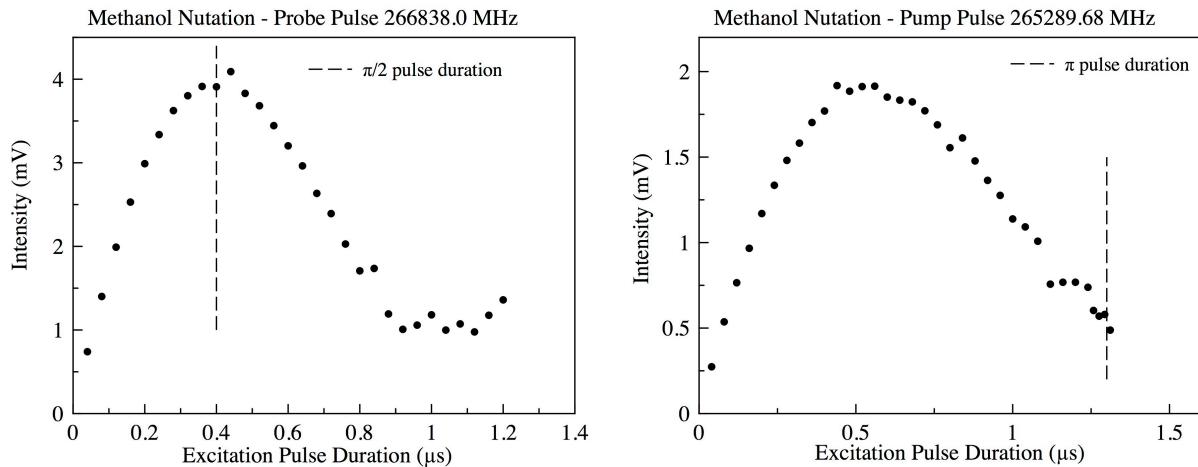


Figure 6. Nutation curves used to measure the $\pi/2$ maximum coherence condition for the probe pulse (400 ns) and the π maximum population inversion for the pump pulse (1300 ns). These are essential parameters for obtaining the best sensitivity in the probe pulse and the best modulation using double resonance excitation.

The pulse sequence described in Figure 4, with the pump and probe pulses tuned to the methanol transitions specified above, was applied to a THF-DMAC solution, a methanol-DMAC solution, and DMAC solution containing both methanol and THF. Five consecutive measurements of the same methanol sample (prepared at 0.3 mg/mL in DMAC) show a double resonance modulation of 75% with standard deviation of 3% (see Figure 7, left panel). The time evolution of the signal is due to vapor adsorbing to the metal surface of the sample cell. Although it allows only one reliable reading for quantitation, the result yields the added benefit of monitoring modulation across a small range of signal strengths. Since the magnitude of the modulation (pump on – pump off) is the metric for quantitation, the reproducibility of the double resonance effect will directly influence the final quantitation precision. However, reproducibility of sample

delivery is the larger effect. Across three independent samples of the same concentration, the methanol probe signal in the static headspace FT-MRR method varies with a relative standard deviation of 11%. THF does not exhibit the same adsorption effect. Five consecutive measurements of THF in DMAc consistently show the same signal strength and zero modulation using the double resonant excitation pulse sequence. One representative spectrum of THF (tuned to the methanol resonance frequency) is shown in the right panel of Figure 7 with excellent background subtraction when methanol is not present (essentially no larger than the spectrometer noise level).

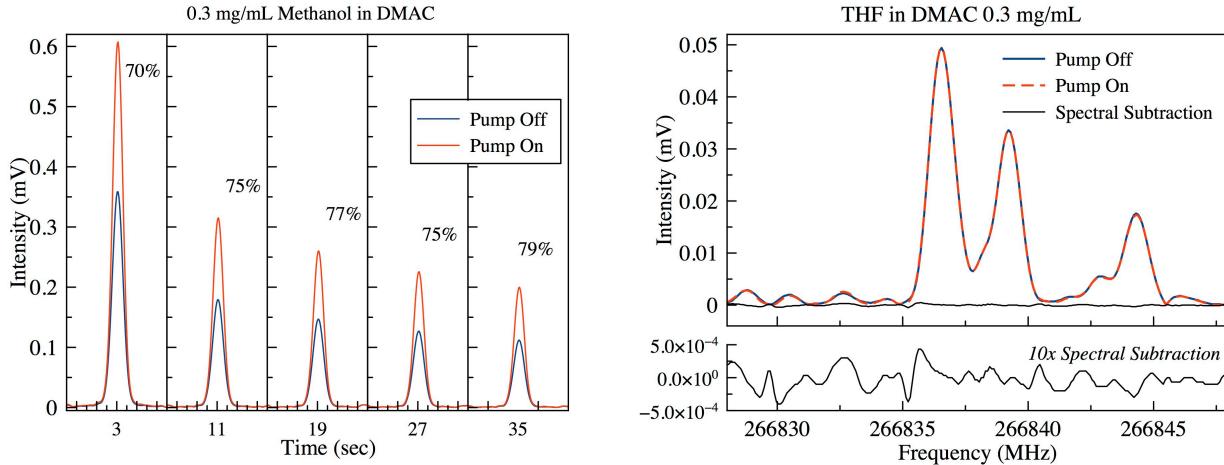


Figure 7. Reference spectra of 0.3 mg/ml methanol in DMAc (left) and 0.3 mg/mL THF in DMAc (right). The five methanol spectra capture (left) capture the double resonance effect as the vapor absorbs to the sample cell wall. The double resonance effect for methanol is a modulation of $75\% \pm 3\%$ and the THF background reproducibility for pump on/off is essentially the sample free noise level of the spectrometer.

A mixture of THF at 0.23 mg/mL and methanol at 0.04 mg/mL in DMAc was then prepared in order to create a scenario where the methanol signal levels are comparable to the THF signals in the overlapping 266838 MHz region. The resulting spectra from on resonant and off resonant pumping are displayed together in Figure 8. Also overlaid in the figure is the background contribution of THF emission determined by scaling the reference spectrum of Figure 6 to the mixture. The remaining methanol emission agrees with that expected from linear scaling the methanol reference measurement at 0.3 mg/mL to 0.04 mg/mL in the mix. The mixture spectrum has a probe signal strength of 0.015 mV and a modulation of 81% versus a reference signal strength of 0.016 mV with 77% modulation.

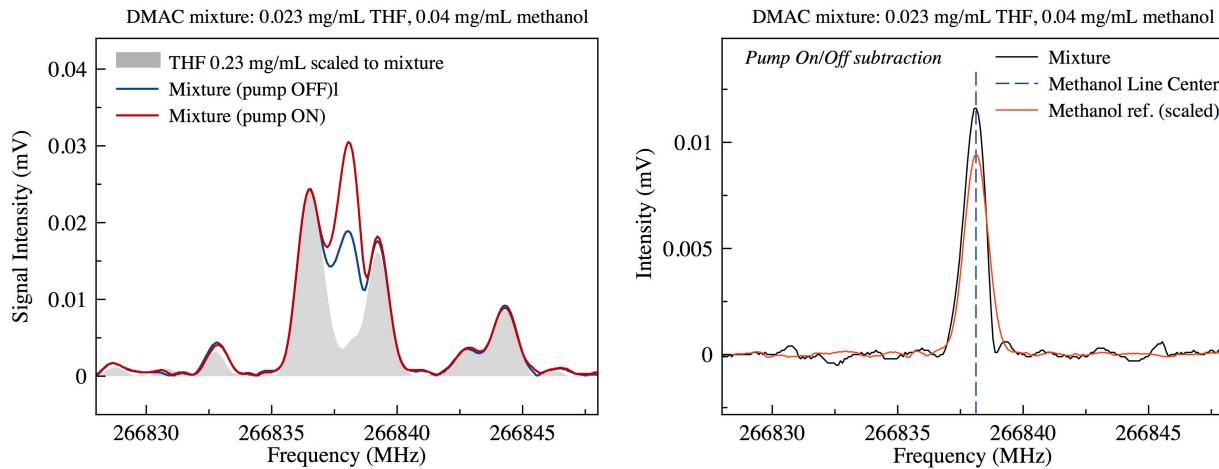


Figure 8. Selective double resonance excitation of a mixture of THF at 0.23 mg/mL and methanol at 0.04 mg/mL in DMAc. The THF reference spectrum in grey (left) is scaled to match the abundance in the mixture. The pump on, pump off subtraction is displayed in the right panel with the expected absolute modulation intensity scaled from the reference spectrum of 0.3 mg/mL methanol in DMAc to the concentration of 0.04 mg/mL in the mixture.

In a real world application, the components of the mixture are not known, therefore subtraction of contributing reference spectra is not possible. With FT-MRR double resonance, the carriers of the interference need not be identified. Subtraction of the normal spectrum from the double resonance excitation spectrum is essentially a subtraction of all signal contributions that are not the molecular emission of interest (see Figure 8, right panel). Knowing the expected fractional double resonance modulation (i.e. $75\% \pm 3\%$) and the magnitude of the experimental modulation, the signal strength of the normal molecular emission can be recovered for quantitation. Alternatively, the absolute magnitude of modulation for a particular concentration can be stored in the targeted library reference as the metric for quantitation.

4. CONCLUSION

This work builds on the development of Fourier techniques for chemical analysis utilizing solid-state millimeter/submillimeter wave light sources. We have designed an instrument which incorporates low-cost microwave synthesizers for targeted chemical analysis. Although the high resolution, broadband FT-MRR spectrum is a highly selective tool for chemical analysis, single line monitoring in combination with selective double resonance excitation is more sensitive and more economical in terms of instrument design for routine impurity analysis. The performance of these new FT-MRR instruments provide a new alternative for chemically selective quantitative analysis that can be performed directly on a complex sample mixture.

The authors thank the National Science Foundation Small Business Innovation Research program for financial support of this work (Award # 1448551)

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